

# HEART

## Editorial

### Grading of cardiac transplant rejection

Cardiac transplantation as a treatment for end stage cardiac failure has become widely accepted, and numerous centres carry out this procedure worldwide. Survival figures have generally improved over the years; the most recent International Society for Heart and Lung Transplantation (ISHLT) registry figures show an overall one year survival of 79% and a patient half life (time to 50% survival) of 8.6 years.<sup>1</sup> Improvements in survival are likely to be multifactorial with the introduction of cyclosporin A undoubtedly being a milestone in immunosuppression. Apart from improvements in immunosuppression, adherence to carefully constructed protocols within transplant centres for patient management has contributed to improvements in quality of life and overall survival. In spite of numerous attempts to find alternative and non-invasive means of monitoring patients, principally for the presence of acute rejection, endomyocardial biopsy remains the gold standard for patient follow up.

Endomyocardial biopsy protocols, with frequent biopsies in the early months and standardised treatments for particular clinical situations, are important in the management of patients. A key element in relation to endomyocardial biopsies is that microscopic appearance of the biopsy specimens should be translated readily into appropriate management. An important component of this is the grading of any rejection in biopsy specimens. Billingham made a decisive contribution to heart transplantation with the introduction of her grading system for cardiac rejection.<sup>2</sup> This system was successfully applied for many years in many units and provided a framework for communication between the reporting pathologists and clinicians managing patients. Some fine tuning was proposed to this grading system and many centres worldwide subsequently chose to modify it, or use their own in-house grading systems.<sup>3,4</sup> Because of an increasing disparity between grading systems used worldwide, and because of the need to standardise diagnosis and compare results between different centres—not least to allow trials of new immunosuppressants—there was clearly a need to develop a new grading system.<sup>5</sup> The aims of this new system were not only standardisation in terms of assessable biopsy fragment numbers and handling in the laboratory, but also the provision of simple numerical classification of histological entities seen under the microscope so that clear treatment thresholds could be established. With that in mind a new ISHLT grading system was produced in 1990<sup>6</sup> (table 1) following a meeting of pathologists, all of whom came from centres with considerable clinical and pathological experience of heart transplantation. This histological grading system was never meant to be prescriptive in terms of where to pitch the treatment threshold. Indeed it allowed for units to experiment to some extent so that the natural history of the various grades of rejection with and without treatment could be established. Nevertheless, based on experience with previous criteria for potentially significant rejection, most units chose to set a treatment threshold for enhanced

immunosuppression at either grade 2 and above or grade 3A and above for cyclosporin A based immunosuppression regimens.<sup>7</sup>

There was an intention by those who produced the 1990 ISHLT grading system to meet subsequently to fine tune and modify the original grades as necessary, and others testing the system in practice supported a revision.<sup>8</sup> A meeting took place in 1994 and a revised grading system was proposed (table 1). The proposals were presented at the ISHLT meeting in 1995 in San Francisco; however, the proposed grading system was never endorsed by the ISHLT and remains unpublished. This was a surprising outcome as the equivalent follow up meeting for lung rejection resulted in the adoption of revised histological criteria by the ISHLT.<sup>9</sup> Those involved in producing the revised cardiac rejection grading system have nevertheless continued to make others in the field aware of it and, as a result of presentations and discussions at the UK National Heart Lung Pathology Group, Suvarna *et al* were stimulated, not only to audit their experiences with 1990 ISHLT grading system, but also to go over to the modified system and audit the effect of this on their patient population.<sup>10</sup>

The changes in the revised system are very simple. As a number of studies had identified the essentially benign nature of grade 2 rejection,<sup>11,12</sup> and it has been shown that most biopsies graded as 2 are actually examples of encroaching endocardial infiltrates<sup>13</sup> (Quilty lesions), a decision was made to abandon this grade and incorporate any biopsies showing a single focus of moderate rejection into a single grade 1 rejection entity, which also amalgamated 1A and 1B from the 1990 system. The justification for this amalgamation was twofold: 1B rejection appears to be relatively unusual as a pure histological pattern; and long term follow up studies indicate that the prognosis is no different from 1A.<sup>11</sup> The latter probably did not contribute much if at all to controversies regarding the adoption of the revised criteria. However, the effective abandonment of grade 2 rejection to some appears to have been a bombshell, as apparently some units continue to view grade 2 rejection as significant and therefore set their treatment threshold at grade 2 rejection and above. Furthermore, several clinical trials of new immunosuppressant regimens were set up using grade 2 as the treatment threshold. In my opinion this threshold is too low, particularly bearing in mind that grade 2 rejection in the vast majority of cases is not in fact rejection in terms of the myocardium but is encroaching endocardial infiltration.<sup>13</sup> The net result on the patient population of setting the treatment threshold too low is to increase the overall burden of immunosuppression. There is abundant evidence from large centres worldwide, including Papworth, that entirely satisfactory results in relation to clinical heart transplantation can be achieved with a treatment threshold set at grade 3A or above (providing adequate biopsies have been taken). Some studies have suggested that grade 2 rejection in the early months post-transplant

Table 1 Grading of cardiac rejection: ISHLT 1990

Old term	Grade	Comments	Proposed simplification (1994)
No rejection	0	Biopsy specimens with very sparse lymphoid infiltrates should be included in this grade	Grade 0
“Mild” rejection	1A	Focal perivascular or interstitial infiltrates. The mild intensity and lack of myocyte damage distinguish this from higher grades.	
“Focal” moderate rejection	1B	Diffuse but sparse infiltrates. As with 1A, there must be no myocyte damage.	Grade 1
	2	One focus only with aggressive infiltration and/or focal myocyte damage. The choice of a single focus as the cut off point from higher grades is arbitrary. In practice, with the amount of tissue usually submitted, one is unlikely to be faced with the problem of biopsy fragments with only two foci.	
USUAL TREATMENT THRESHOLD			
“Low” moderate rejection	3A	Multifocal aggressive infiltrates and/or myocyte damage. The multiple foci may be present in only one fragment or scattered throughout several fragments.	Grade 3A
	3B	Diffuse inflammatory process. The intensity of the lymphoid infiltrate varies considerably; it may be little more than 1B. The important feature distinguishing this grade is the presence of myocyte damage. This damage must be present in at least two fragments but some degree of infiltration is present in most fragments.	Grade 3B
“Severe acute” rejection	4	A diffuse and polymorphous infiltrate with or without oedema, haemorrhage, and vasculitis. The infiltrate is more intense and more widespread than 3B, and myocyte damage is conspicuous. There are often neutrophils and/or haemorrhage, although neither is essential for classification as this grade.	Grade 4

may progress to higher grades of rejection.<sup>14</sup> Such data, however, is fundamentally flawed because acute cellular rejection involving the deep myocardium is much more likely to occur in the first few months, and this is the period during which patients are having repeated protocol biopsies and, to some extent, the more you look for rejection the more of it you are likely to find!

The paper by Suvarna *et al* establishes that it is perfectly safe within a centre to adopt the 1994 criteria<sup>10</sup>; furthermore, in abandoning grade 2 rejection there is no corresponding increase in higher grades of rejection, which could be predicted if lack of reporting of grade 2 was likely to lead to evolution to a higher grade. The paper is a very honest audit of the learning curve that many pathologists must have travelled when they first started evaluating cardiac transplant biopsy specimens, and when they started to use a new grading system. It is hardly surprising that there was a learning curve given that pathologists were somehow expected to know how to use the 1990 grading system simply by reading an account of it in a journal. The findings will be useful to the steady stream of pathologists evaluating biopsy specimens of this kind for the first time. It is also worthwhile to make clinicians fully aware of the potential fallibility of ascribing a numerical grade of rejection. This, however, should not be to the extent to encourage the deplorable practice of giving enhanced immunosuppression in the face of adequate negative biopsies.

I find the suggestion of further simplification in terms of having only three grades (grade 0, low grade, and high grade)<sup>10</sup> an attractive one, not least because anything that improves communication between pathologists and physicians is likely to improve patient management. It might at first seem that this suggestion is retrograde and amounts to simply re-adopting the original Billingham criteria<sup>2</sup>; however, this could not be further from the truth. The introduction of the 1990 grading system allowed for the definition of a number of recognisable histological entities and their translation into numerical grades. This in turn allowed for a number of follow up studies that defined the significance in terms of likely progression and long term consequences of those various grades. Although there is only a low grade and a high grade proposed, each of these two grades from the pathologist's point of view includes a number of clearly recognisable histological entities. Therefore, this represents a considerable progression from the original Billingham criteria.

A simplified grading system, while potentially improving communication between pathologists and clinicians, does not prevent the reporting of various unusual changes that do not fit satisfactorily into a grading system. The use of free text in a histological report is invaluable, and it would be a sad day if the pathologist simply pressed a button at the microscope to record one of three histological grades. The ISHLT 1990 grading system has been widely adopted but may have served its purpose in allowing a number of histological entities to be tested in the field. Now is the time to modify and simplify it, and the paper by Suvarna *et al* illustrates the potential role of groups such as the UK National Heart Lung Transplant Pathology Group in promoting and auditing such modifications.

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- Hosenpud JD, Bennett LE, Keck BM, *et al*. The registry of the International Society for Heart and Lung Transplantation: fourteenth official report—1997. *J Heart Lung Transplant* 1997;16:691–712.
- Billingham ME. Diagnosis of cardiac rejection by endomyocardial biopsy. *Heart Transplant* 1982;1:25–30.
- Pomerance A, Stovin PGI. Heart transplant pathology: the British experience. *J Clin Pathol* 1985;38:146–59.
- Kennitz J, Cohnert T, Schäfers H-J, *et al*. A classification of cardiac allograft rejection. A modification of the classification by Billingham. *Am J Surg Pathol* 1987;11:7:503–15.
- Billingham ME. Dilemma of variety of histopathological grading systems for acute cardiac allograft rejection by endomyocardial biopsy. *J Heart Transplant* 1989;9:272–6.
- Billingham ME, Cary NRB, Hammond ME, *et al*. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. *J Heart Transplant* 1990;6:587–93.
- Balk AH, Zondervan PE, van der Meer P, *et al*. Effect of adopting a new histological grading system of acute rejection after heart transplantation. *Heart* 1997;78:603–67.
- Nielsen H, Sørensen FB, Nielsen B, *et al*. Reproducibility of the acute rejection diagnosis in human cardiac allografts. The Stanford classification and the international grading system. *J Heart Transplant* 1993;12:239–43.
- Yousem SA, Berry GJ, Cagle PT, *et al*. A revision of the 1990 working formulation for the classification of lung allograft rejection. *J Heart Lung Transplant* 1996;15:1–15.
- Suvarna SK, Kennedy A, Ciulli, *et al*. Revision of the 1990 working formulation for cardiac allograft rejection: the Sheffield experience. *Heart* 1998;79:432–6.
- Riseq MN, Masek MA, Billingham ME. Acute rejection: significance of lapsed time post transplant. *J Heart Lung Transplant* 1994;13:862–8.
- Winters G, Loh E, Schoen F. Natural history of focal moderate cardiac allograft rejection. Is treatment warranted? *Circulation* 1995;91:1975–80.
- Fishbein MC, Bell G, Lones MA, *et al*. Grade 2 cellular rejection: does it exist? *J Heart Lung Transplant* 1994;13:1051–7.
- El-Gamel A, Doran H, Rahman A, *et al*. Clinical importance of grade 2 cellular heart rejection [letter]. *J Heart Lung Transplant* 1996;15:319–21.